
Contents

Acknowledgements	v
Abstract	vii
1 Introduction	1
1.1 Structure and classification of cells	3
1.2 History of animal electricity	4
1.3 Field exposure of cells and biological samples	6
1.4 Purpose of the work	8
1.5 Outline	10
2 Impedance spectroscopy	13
2.1 Impedance, permittivity and conductivity	15
2.2 Cellular impedance recording	16
2.3 Electrode configurations for EIS	18
2.3.1 Two-electrode configuration	19
2.3.2 Three-electrode configuration	19
2.3.3 Four-electrode configuration	19
2.3.4 Accuracy contour plots	20
2.4 Equivalent circuit components	20
2.4.1 Resistance, capacitance and inductance	21
2.4.2 The Warburg element	22
2.4.3 The constant-phase element	22
2.4.4 Faradaic and non-faradaic processes	23
2.4.5 Double-layer capacitance	24
2.5 Equivalent circuit models	25
2.5.1 Simple electrode	25
2.5.2 Randles cell	26
2.5.3 Circuits with two or three frequency relaxations	26
2.5.4 Basic models for cell suspensions	28
2.6 Simulation of a 3D cell culture	29
2.7 Commercial tools for fitting	32
2.8 Impedance fitting toolbox	34

2.8.1	Fitting algorithms	35
2.8.2	Circuit strings and predefined models	36
2.8.3	Error estimation	37
2.8.4	Fitting example	38
2.9	Chapter conclusion	40
3	Applications of impedance spectroscopy	41
3.1	Impedance response of tumor and healthy cells	41
3.2	Liquid samples infected with bacteria	46
3.3	Fruit ripening	47
3.4	Cell viability	49
3.5	Lactate concentration in athletes	52
3.5.1	The Krebs and Cori cycles	53
3.5.2	In-vitro lactate measurements	54
3.5.3	Blood lactate measurements	56
3.5.4	Impedance measurements with sensor	57
3.6	Chapter conclusion	58
4	Impedance measurement circuits	59
4.1	Wheatstone bridge	60
4.2	Auto-balancing bridge method	61
4.3	Frequency response analysis method	63
4.4	Network analysis method	64
4.5	Chapter conclusion	65
5	Demonstrator of a portable impedance spectrometer	67
5.1	Block diagram	68
5.2	Design of the analog circuitry	69
5.3	Design of the digital logic	70
5.4	Frequency response measurements	70
5.5	Experiments with constant known loads	71
5.6	Experiments with yeast	72
5.7	Chapter conclusion	73
6	Miniaturized portable impedance measurement system	75
6.1	Chip architecture	76
6.1.1	Configuration register	76
6.1.2	Internal oscillator	77
6.1.3	Low-pass filters	78
6.1.4	Analog-to-digital converters	79
6.1.5	Current-to-voltage converter	80
6.2	Impedance calculation example	82
6.3	LabVIEW Implementation	83
6.3.1	Graphical user interface	85
6.3.2	Discrete Fourier Transform	86

6.4	Impedance measurements	87
6.5	Phase measurements	88
6.6	Biological experiments	89
6.6.1	Experiments with yeast	89
6.6.2	Experiments with porcine chondrocytes	91
6.7	Chapter conclusion	92
7	High frequency stimulation	93
7.1	Chip architecture	94
7.1.1	Quadrature oscillator	94
7.1.2	Emitter followers	96
7.1.3	Cherry-Hooper amplifier	97
7.1.4	Gilbert mixers	97
7.2	Impedance calculation	98
7.3	Simulations of an RC impedance load	99
7.4	DC operating point of the VCO	101
7.5	Inductor S-parameters	102
7.5.1	Inductor simulation using HFSS	102
7.5.2	SOLT Callibration	103
7.5.3	Inductor measurements	104
7.6	Oscillator measurements	105
7.7	Chapter conclusion	108
8	High frequency stimulation redesign	111
8.1	Chip architecture and simulations	112
8.2	Assembly technologies for bare die ASICs	113
8.2.1	Flip chip bonding	113
8.2.2	Bond wire inductance	115
8.2.3	Simulations in HFSS	116
8.3	Test board assembly	117
8.4	Oscillator frequency and amplitude	119
8.5	DC operating point of the VCO	121
8.6	Simulation of an ESD error	121
8.7	Measurement of cell cultures	123
8.8	Simulation of the microstrip line	125
8.9	Chapter conclusion	127
9	Conclusions and outlook	131
A	ASIC bonding plans	135
A.1	ASIC 1	135
A.2	ASIC 2	137
A.3	ASIC 3	139

Bibliography	141
List of Figures	153
List of Tables	157
List of Abbreviations	159
List of Symbols	161